ANNEX H TO DOD SMALLPOX RESPONSE PLAN 14 Jun 2002
MEDICAL CARE OF ADVERSE EVENTS AFTER SMALLPOX VACCINATION

REFERENCES.

a. CDC Interim Smallpox Response Plan, Annex 3. Vaccine Adverse Event Reporting. http://www.bt.cdc.gov/DocumentsApp/Smallpox/RPG/annex/annex-3.doc.

b. Advisory Committee on Immunization Practices. Vaccinia (smallpox) vaccine. *MMWR* 2001;50(RR-10):1-25. http://www.cdc.gov/mmwr/PDF/rr/rr5010.pdf [Appendix J-5].

c. United States Army Medical Command. Clinical Guidelines For Managing Adverse Events After Vaccination. Falls Church, VA, June 2002.

d. United States Army Medical Command. "How-To" Guide for Command Surgeons: Implementation Guidelines for Investigational New Drug (IND) Protocols. Falls Church, VA, May 2002.

e. United States Army Medical Command. "How To" Guide for Unit Leaders and Unit Health Care Providers: Implementation Guidelines for Investigational New Drug (IND) Protocols. Falls Church, VA, May 2002.

f. United States Army Medical Command. "How To" Guide for Investigational New Drug (IND) Protocols, Supplement: Vaccinia Immune Globulin (IND # pending). Falls Church, VA, publication pending.

g. United States Army Medical Command. "How To" Guide for Investigational New Drug (IND) Protocols, Supplement: Cidofovir (Vistide®, Gilead) To Treat Vaccinia Reactions (IND # pending). Falls Church, VA, publication pending.

1. General. This DoD Annex augments CDC Annex 3. Appendix H-1 summarizes CDC Annex 3 and this DoD Annex on one page.

a. Mission. Health-care workers will take actions warranted to treat people who develop severe adverse events after smallpox vaccination.

b. Assumptions.

(1) An increased use of smallpox vaccine is expected, as part of the national program to prepare for the contingency of a smallpox outbreak. Mild to moderate adverse events after smallpox vaccination can be managed according to guidelines in references a, b, and c.

(2) Serious adverse events (AEs) associated with smallpox vaccine are expected, with an overall frequency of ~ 50 serious AEs per 1,000,000 vaccinations. Mild and moderate AEs occur more frequently after smallpox vaccination. The unique adverse events that follow smallpox vaccination chiefly involve progressive or complicated disease with this live-virus vaccine.

(3) Vaccinia immune globulin (VIG) was FDA-licensed until the 1990s as an effective treatment for some adverse events after smallpox vaccination (e.g., eczema vaccinatum, progressive vaccinia, ocular vaccinia, afebrile-"toxic" generalized vaccinia) (Appendix H-2). VIG is currently available only under an investigational new drug (IND) protocol (references b and f). VIG is in short supply.

(4) Although no human efficacy data are available yet, cidofovir (*Vistide*, Gilead Sciences, www.gilead.com/wt/sec/vistide, Appendix H-3) may be effective in treating adverse events associated with invasive or progressive disease after smallpox vaccination.

c. Planning Factors.

(1) Education and Awareness. Prompt recognition of serious adverse events after smallpox vaccination, especially those that benefit from specific therapy, is integral to the training of smallpox-vaccination teams and others who provide primary care. Once a possible serious adverse event is recognized, vaccination teams and primary-care providers must have access to specialists in infectious diseases, dermatology, and/or allergy-immunology.

(2) Access to VIG and Cidofovir.

(a) MTFs will not use on-hand stocks of VIG or cidofovir to treat patients infected with variola virus, nor order them from other sources, without first coordinating with the US Army Medical Research Institute of Infectious Diseases (USAMRIID).

(b) USAMRIID will establish a common point of access for telephonic requests for use of VIG or cidofovir for a named patient by a physician willing to comply with IND requirements (references d, e, f, and g). Access to cidofovir for eligible patients will be facilitated by regional treatment teams (T-Teams). Civilian healthcare providers should contact the CDC Drug Service for VIG or cidofovir: CDC Drug Service, National Center for Infectious Diseases, Mail stop D-09, Atlanta, GA 30333; 404-639-3670, fax 404-639-3717.

(3) Training. Treatment teams will be trained in the requirements of IND protocols in general and the cidofovir treatment protocol in particular, to allow prompt use of this agent. USAMRMC and USAMRIID will coordinate training.

(4) Personnel Resources. If warranted by available resources, a specialized treatment team may travel to the MTF to assist with cidofovir administration. The gaining MTF will assign additional personnel to the treatment team, as requested by the treating physician(s). Additional DoD assets will be assigned, if requirements extend beyond the capabilities of the local MTF. Additional details about composition of treatment teams appear in Annex G.

(5) Other Medications. If therapeutic approaches with VIG or cidofovir are inadequate, clinicians may be inclined to try other therapeutic modalities unavailable when routine smallpox vaccinations ceased in the 1970s and 1980s (e.g., immune globulin intravenous as an immunomodulator to treat encephalitis). Little or no data may exist to support the safety or effectiveness of such approaches and no Federal agency sanctions their use. Nonetheless, DoD clinicians reserve their individual prerogatives and responsibilities in the clinical practice of medicine for individual patients.

d. Coordinating Instructions.

(1) Command Relationships. The treatment team will be assigned under the operational control (OPCON) of the local MTF commander.

(2) Communication. No information will be conveyed to other external sources, including the media, without command approval. If working in coordination with local treatment teams, no information will be conveyed to other external sources, including the media, without approval of, or simultaneous presentation with, the coordinating agency (CONUS--CDC, OCONUS--WHO).

(3) VIG investigators and cidofovir investigators will coordinate with the Walter Reed National Vaccine Healthcare Center (VHC, 301-782-0411, DSN 662-0411) on status of individuals treated with VIG or cidofovir under IND protocol. Treatment teams, investigators, and the VHC will assist in centralized tracking and case management and provide coordination with CDC's Clinical Immunization Safety Assessment (CISA) centers of excellence.

e. Legal Considerations.

(1) All use of IND agents will be performed in accordance with IRB-approved guidelines and FDA regulations (see references d, e, f, and Appendix G-2). MTFs will provide personnel and supply resources to the treatment teams to satisfy regulatory requirements.

(2) Adverse events due to vaccination for occupational purposes are covered under provisions of worker's compensation benefits. Civilian employees should seek counsel from occupational health clinics in this regard.

2. Execution.

a. Concept of Operations.

(1) Recognition of a serious adverse event after smallpox vaccination will be infrequent, but of high consequence to the patient affected. Based on criteria in references a and b, the attending physician will consult with an infectious-disease, dermatology, and/or allergy-immunology specialist. If warranted the specialist may request use of either VIG or cidofovir, according to clinical circumstances, from USAMRIID, the unit staffed with the principal investigators for the IND protocols for these agents.

(2) Patients will be treated by a physician registered as a subinvestigator on the applicable IND protocol. Patients will be treated at the earliest possible opportunity, at the closest MTF possible. Movement of patients to capable MTFs, and treatment teams to the same MTFs, will be expedited. Patient consent must be obtained before administration. See also Appendix G-2, for exceptions for unconscious patients.

(3) Patients with appropriate indications (i.e., not encephalitis, not keratitis) will be treated using available supplies of VIG under IND until the VIG supply is exhausted. Cidofovir, also under IND, will then be used for any subsequent serious adverse events (Appendix H-3). The rationale for this approach is that less effectiveness data is available for cidofovir, which is more prone to inducing adverse events than VIG. Nonetheless, cidofovir is in greater supply than VIG.

(4) Actual protocol use of these agents is specified in the pertinent treatment protocols (references f and g), including dosage, expected side effects, and regulatory and reporting issues.

(5) Because of the administrative burden of implementing an IND protocol, and cidofovir's intravenous route of administration, multidisciplinary treatment teams may travel to an MTF to administer the IND product and assist with patient care. During a smallpox outbreak, prior vaccination against smallpox will be a condition of membership on these teams.

b. Tasks and Responsibilities.

(1) Recognition of serious adverse events after smallpox vaccination is the responsibility of smallpox vaccination teams and primary-care providers. Any member of the medical team or the patient or patient's contacts can alert the system to the possible presence of a vaccine-related adverse event.

(2) Once a definite or probable diagnosis of a medication-indicating adverse event has been made by a qualified provider (e.g., infectious-disease, dermatology, allergy-immunology physician), that provider may request use of VIG or cidofovir for a named patient by telephoning USAMRIID at 1-800-USA-RIID [after duty hours, page the USAMRIID staff duty officer at 301-631-4393 or the USAMRMC staff duty officer at 301-

619-6092]. Civilian healthcare providers contact the CDC Drug Service for VIG at 404-639-3670. USAMRIID will coordinate with treatment teams, which will travel to the MTF caring for the diagnosed smallpox patient. These teams will be responsible for the treatment of patients with the indicated medications. IND-specific procedures will be followed carefully.

(3) The MTF will provide routine medical care in accordance with standard practice, with laboratory, radiology, and pathology support. If the patient is treated with an IND agent, the treating team will have responsibility for the completion and maintenance of records and reports, as well as the processing or packaging of pathologic or autopsy materials.

(4) MTF commanders will be responsible for transporting patients between MTFs; provision of ancillary supply and personnel resources to treatment teams; pharmacy and laboratory support; and communication support.

(5) The service member's unit will be responsible for initial transportation to the first-level MTF. Once within the medical system, it will be the responsibility of the medical-evacuation system for further patient transportation as needed.

c. Reporting.

(1) T-team leaders will periodically brief the MTF commander on the status of patients with post-vaccination adverse events, at a frequency directed by the commander. Similar briefings will occur for and at the direction of the commander, USAMRIID.

(2) IND protocol reports will be submitted as detailed in the protocols.

(3) There is no need to report adverse events to VAERS that involve smallpox vaccine treated with vaccinia immune globulin (VIG) or cidofovir under IND protocol. The FDA will review all clinical data for patients treated with VIG or cidofovir under IND protocol under separate report filings. Filing reports to the Vaccine Adverse Event Reporting System (VAERS) in cases involving VIG or cidofovir under IND protocol is inappropriate, because filing a VAERS report will lead to double-counting of the case.

3. Operational Constraints.

a. Equipment. No specialized equipment other than routine medical care in MTFs will be required.

b. Training. Treatment teams will be trained in the requirements of IND protocols in general and the VIG and cidofovir treatment protocols in particular, to allow prompt use of this agent. USAMRMC and USAMRIID will coordinate such training. Periodic alert exercises, without travel, will be performed to sustain team proficiency. During smallpox outbreaks, prior vaccination against smallpox will be a condition of membership on these teams.

c. Control of IND Agents. MTF pharmacy support to treatment teams will include storage (see below), control, and security for both cidofovir and locally available medications. Pharmacy assets on the treatment teams will prepare and dispense cidofovir for the treatment team's use. Emergency use of an investigational drug for a named patient will comply with notification requirements to U.S. Army Medical Command, in accordance with Army Regulation 40-7 (Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances, 4 January 1991), paragraph 4-9, and comparable regulations in other military Services.

d. Medical Care of the Patient. General medical supportive care to a patient with an adverse event after vaccination will be given by the attending team organic to the MTF, supplemented by the specific therapy given by the assigned treatment team, supplemented with MTF personnel as needed.

4. Administration and Logistics.

a. Shipping and Distribution. Either the T-Teams will transport the VIG or cidofovir themselves, or they will coordinate with the US Army Medical Materiel Agency (USAMMA) for transportation (see Annex I).

b. Supply and Storage. Supplies of VIG or cidofovir, delivered from USAMRIID, will be stored and maintained by the MTF pharmacy under the appropriate environmental conditions.

c. MTFs will provide administrative support for protocol performance by the treatment teams (e.g., office space, copying, automation, communication support).

5. Special Situations.

a. Healthcare providers will attempt to periodically observe smallpox vaccine recipients through the duration of vaccine take and injection-site resolution. Nevertheless, recipients may be required to travel before this vulnerable window for complications has passed.

b. All situations in which a potential adverse event after vaccination is recognized in a recipient while outside of CONUS, or underway either in CONUS or outside of CONUS, should be handled by directing or transporting the recipient to the nearest MTF in an expedited manner. Once arrived, the medical consultation process described above will be implemented.

APPENDIX H-1
Medical Care Of Adverse Events After Smallpox Vaccination – Summary.

1. Recognition of a serious adverse event after smallpox vaccination will be infrequent, but of high consequence to the patient. The attending physician will consult with an infectious-disease, dermatology, and/or allergy-immunology specialist. If warranted the specialist may request use of either vaccinia immune globulin (VIG) or cidofovir.

2. The US Army Medical Research & Materiel Command (USAMRMC) is applying to the Food & Drug Administration (FDA) for permission to use cidofovir (*Vistide*, Gilead Sciences, Appendix H-3) under an investigational new drug (IND) protocol to treat adverse events after smallpox vaccination. This annex assumes FDA will approve this IND protocol.

3. Patients with appropriate indications (e.g., eczema vaccinatum, progressive vaccinia, ocular vaccinia, febrile-"toxic" generalized vaccinia) (i.e., not encephalitis, not keratitis) will be treated using available supplies of VIG under IND until the VIG supply is exhausted. Cidofovir will then be used under IND for any subsequent serious adverse events. Less effectiveness data is available for cidofovir, which is more prone to inducing adverse events than VIG. Nonetheless, cidofovir may be in greater supply than VIG.

4. Because of the administrative burden of implementing an IND protocol, and cidofovir's intravenous route of administration, multidisciplinary treatment teams may travel to an MTF to administer cidofovir and assist with patient care. During a smallpox outbreak, prior vaccination against smallpox will be a condition of membership on these teams.

5. Once a definite or probable diagnosis of a medication-indicating adverse event has been made by a qualified provider (e.g., infectious-disease, dermatology, allergy-immunology physician), that provider may request use of VIG or cidofovir for a named patient by telephoning USAMRIID at 1-800-USA-RIID. After duty hours, page the USAMRIID staff duty officer at 301-631-4393 or the USAMRMC staff duty officer at 301-619-6092.

6. USAMRIID will coordinate with these treatment teams (T-teams), which will travel to the MTF caring for the patient. IND-specific procedures will be followed carefully. The treatment team will be assigned under the operational control (OPCON) of the local MTF commander.

7. Treatment team leaders will periodically brief the MTF commander on the status of patients, at a frequency directed by the commander. Similar briefings will occur for and at the direction of the commander, USAMRIID. Treatment team leaders and IND investigators will submit IND protocol reports as required by the FDA.

APPENDIX H-2
Product Labeling for Vaccinia Immune Globulin (VIG).

[reprinted verbatim from Hyland Therapeutics Division's VIG product labeling, circa 1983. Note that production methods in that era did not include viral-inactivation steps.]

Hyland®
Vaccinia Immune Globulin (Human)

DESCRIPTION

HYLAND Vaccinia Immune Globulin (Human) is a sterile 16.5 (±1.5) percent solution of the immunoglobulin fraction of plasma from individuals who were immunized with vaccinia virus. The solution is isotonic and contains 0.3M glycine as a stabilizer. It contains 0.01% thimerosal (a mercury derivative) as a preservative and 0 1% sodium chloride.

This product meets the FDA potency requirements for vaccinia antibody.

Each unit of plasma used in the preparation of this product has been found to be nonreactive for hepatitis B surface antigen (HBsAg) by counterelectrophoresis or radioimmunoassay. The product is prepared by the cold ethanol fractionation method; no instance of hepatitis transmission has been reported from the use of human immune globulins when prepared by this method.

This product has been processed and tested in accordance with requirements established by the Food and Drug Administration and is distributed under U.S. License No. 140.

INDICATIONS

Smallpox -Prevention or Modification:

Administration of Vaccinia Immune Globulin (Human) in conjunction with simultaneous vaccination or revaccination has been shown to reduce the incidence of smallpox in exposed individuals.[1]

Vaccinia Infections -Prevention or Modification:

Vaccinia Immune Globulin (Human) may be indicated in the following circumstances to prevent or modify aberrant infections induced by smallpox vaccine:[2-5]

a. Accidental implantation of vaccinia virus in eyes, mouth, or other areas where vaccinia infection would constitute a special hazard

b. Accidental vaccinia exposure of children who have extensive skin lesions such as eczema, burns, impetigo, or varicella.

c. Eczematous children where vaccination is indicated due to risk of exposure to smallpox.

Treatment of Postvaccinal Complications:

Vaccinia Immune Globulin (Human) may be effective for use in the following conditions: eczema vaccinatum, vaccinia necrosum, severe generalized vaccinia, vaccinia infections of the eyes or mouth, and vaccinia infections in the presence of other skin lesions such as burns, impetigo, varicella-zoster, or poison ivy.

This product is not of value in the treatment of postvaccinal encephalitis.

CONTRAINDICATIONS

Vaccinia Immune Globulin (Human) is contraindicated for use in the presence of vaccinal keratitis. The administration of a similar preparation in rabbits with vaccinal keratitis has been shown to cause increased scarring.[6]

WARNINGS

Do not give intravenously; this preparation is for intramuscular use only. Do not use if turbid.

PRECAUTIONS

A separate sterile syringe and needle or single-use disposable unit must be used for each individual patient to prevent the possible transmission of hepatitis or other infectious agents from one patient to another.

After cleansing the site for injection and inserting the needle in a muscle, draw back on the plunger of the syringe before injection in order to be certain that the needle is not in a blood vessel.

ADVERSE REACTIONS

A few instances of allergic or anaphylactoid systemic reactions have been reported following intramuscular injection of human immunoglobulin preparations. It is advisable that epinephrine or other suitable medication be available for treating such reactions should they occur.

Occasionally local tenderness and stiffness occur, persisting from a few hours to 1 to 2 days following injection (When the dosage is 10 ml or more, it should be divided and injected at 2 or more sites in order to reduce the trauma of injection).

DOSAGE

Smallpox - Prevention or Modification:

A dose of 0.3 ml per kg of body weight should be given within 24 hours of exposure. Exposed individuals should be simultaneously vaccinated or revaccinated with smallpox vaccine unless otherwise contraindicated.

Vaccinia Infections -Prevention or Modification:

A dose of 0.3 ml per kg of body weight should be given simultaneously with smallpox vaccination. In cases of accidental exposure to vaccinia virus, this dosage should be given as soon as possible after exposure has occurred.

Treatment of Postvaccinal Complications:

A dose of 0.6 ml per kg of body weight should be administered as soon as possible after symptoms appear. This dose may be repeated, depending upon the severity of symptoms and response to treatment.

No therapeutic effect may be expected from the use of this product in postvaccinal encephalitis.

ADMINISTRATION

Vaccinia Immune Globulin (Human) is to be administered intramuscularly, preferably in the buttock or the anterolateral aspect of the thigh.

When the dosage is 10 ml or more, it should be divided and injected at 2 or more sites.

HOW SUPPLIED

HYLAND Vaccinia Immune Globulin (Human) is available in a 5-ml size.

REFERENCES

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2. Kempe CH: Studies on smallpox and complications of smallpox vaccination. Pediatrics 26:176, 1960
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5. Report of the Committee on the Control of Infectious Diseases, 16th Ed. Evanston, Amer Acad Pediat, 1970, p. 14
6. Fulginiti VA, Winograd LA, Jackson M, et al: Therapy for experimental vaccinal keratitis: Effect of idoxuridine and VIG. Arch Ophthal 74:539, 1965

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APPENDIX H-3
Product Labeling for Cidofovir.

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